REMARKS

Claims 1-8, 10, 22-26, 40-46, 48, 57-59, and 61 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Deihl (WO 9413280) in view of Swaminathan (WO 9733621) and further in view of the Physician's Desk Reference ("PDR"). This rejection is respectfully traversed.

The Office Action acknowledges receipt of the Declaration of Dr. Frank Blondino and admits that the detailed results of clinical studies show that the buccal spray dosage form has a much better pharmacokinetic profile than its tablet or other oral dosage forms. Office Action at 12. However, the Office Action continues: "It has been established that the spray forms (buccal, nasal, or pulmonary) have a faster onset of action, eliminate the first pass effect, thus resulting in less side effects and a much lower amount of medicament is required to achieve the therapeutic effect." In support, the Office Action states:

> Diehl teaches and suggests that it is highly advantageous to provide a composition for buccal absorption. Diehl states that I have now discovered liquid analgesic compositions and methods of administering analgesic compounds which are conveniently and inexpensively prepared, conveniently administered, and which may provide the desired physiological effect at a lower total dose than that obtained by use of prior tabletted or swallowed liquid compositions.

Office Action at 12, emphasis added.

The Applicant disagrees that Deihl can support the Office Action's assertions about what had "been established" prior to the Blondino Declaration. First, Deihl says nothing about fast onset of any drug via buccal spray. Second, Deihl says nothing about zolpidem; and third, says nothing about use of a lower dosage by buccal spray to achieve a therapeutic effect for zolpidem. These features are now incorporated as limitations in the amended claims. Even for the two particular analgesic compounds of Deihl, Deihl only says that the desired effect "may" be provided by buccal spray. The actual examples of Deihl are clear, however, that no such effect could have been produced, because Deihl fails to achieve transmucosal oral absorption of any pharmacologically effective amount. Applicants question how one of ordinary skill could conclude that Deihl shows

that "a much lower amount of medicament is required to achieve a therapeutic effect" (Office Action at 12), when Deihl achieves no therapeutic effect at all.

As a result, the mere assertion in Deihl that this therapeutic effect "may" occur at a lower dose is insufficient to establish obviousness for an entirely unrelated compound, particularly where (as here) Deihl fails to substantiate this "may" occurrence, and where (as here) Applicant has provided actual clinical data to demonstrate that not only does the claimed buccal spray method with zolpidem achieve a therapeutic effect, but in addition this effect is achieved at a lower dose of zolpidem, and with faster onset of action. These features are now incorporated as limitations in the amended claims.

Regarding faster onset as established by the Blondino Declaration, the Office Action does not provide any cite to any portion of Deihl to support the assertion of the Office Action, and none exists.

Regarding lower dose to achieve therapeutic or pharmacologic effect, the Office Action is mistaken for all of the reasons set forth below, including that the pending claims all require transmucosal absorption of a pharmacologically effective amount via a method for administration of a buccal spray. Deihl fails to achieve any therapeutic effect, much less any such effect at a hypothetical lower dose. A simple check of the maximum blood levels of Deihl compared to the minimum required for therapeutic effect shows that Deihl could not possibly have achieved any therapeutic effect by buccal spray.

According to the Office Action, "Applicant is arguing limitations not claimed. Claims are drawn to a method of **administering** a composition ... by spraying the oral mucosa ...." Office Action at p. 10, emphasis in original. The Office Action is incorrect in this regard, because all of the claims explicitly require "transmucosal absorption of a pharmacologically effective amount of zolpidem through the oral mucosa to the systemic circulatory system." This claim language cannot be ignored and establishes a significant difference over the disclosure of Deihl. Accordingly,

Applicant's arguments are based on the limitations of all claims, each of which distinguishes Deihl for at least this reason.

Even assuming, for the sake of argument, that buccal spray administration of Dehil's actives, acetaminophen or ibuprofen, can achieve higher bioavailability than conventional dosage routes, Deihl still fails to disclose "transmucosal absorption of a pharmacologically effective amount."

Deihl is plainly directed to spraying sub-therapeutic amounts. Deihl states that a patient sprays four measured sprays into the mouth. Each spray is 50 microliters and contains 1 milligram of acetaminophen or ibuprofen. This may be repeated once after five minutes. That is, Deihl teaches spraying a total dose of 4-8 milligrams of acetaminophen or ibuprofen. Deihl at 5.

The minimum conventional oral dosage for acetaminophen is 320 milligrams for adults, with about 88% bioavailability. For ibuprofen the minimum oral dosage for adults is 400 milligrams with about 80% bioavailability. According to GOODMAN AND GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 10th ed., the minimum oral tablet dose of acetaminophen (320 mg) at 88% bioavailability results in 281 mg acetaminophen available systemically. This is the minimum systemic amount for achieving effective therapy no matter how administered, because the bioavailability percentage serves to factor out any differences due to different routes of administration. Accordingly, if Deihl's buccal spray method does not achieve systemic levels of at least 281 mg acetaminophen, Deihl's method does not result in a pharmacologically effective amount in the systemic circulation.

Deihl only discloses, at most (even incorrectly assuming 100% bioavailability), administering 8 mg acetaminophen. Therefore, Deihl does not achieve the claimed "transmucosal absorption of a pharmacologically effective amount" by oral spray, as required by each of Applicant's methods claims.

Similarly, the minimum conventional oral dose of ibuprofen (400 mg) at 80% bioavailability results in 320 mg ibuprofen available systemically. This is the minimum systemic amount for effective therapy no matter how administered, because again the bioavailability percentage serves to factor out any differences due to different routes of administration. Accordingly, if Deihl does not achieve systemic levels of at least 320 mg ibuprofen, Deihl does not disclose a method involving transmucosal absorption of any pharmacologically effective amount.

Since Deihl only discloses, at most (even incorrectly assuming 100% bioavailability) 8 mg ibuprofen, Deihl again fails to achieve the claimed "transmucosal absorption of a pharmacologically effective amount."

Furthermore, even presuming, for the sake of argument, that one of ordinary skill would accept Deihl's assertion that "alleviation of headaches can be obtained by administration of only approximately 1/20th of the dose normally recommended for tabletted analgesics," Deihl's buccal sprays also fail to administer at least 1/20th of such amounts. One twentieth of 320 mg is 16 mg of acetaminophen; and 1/20th of 400 mg is 20 mg of ibuprofen. In contrast, Deihl delivers only 8 mg, which is a small fraction of these amounts.

Consequently, even using Deihl's own best case scenarios, one of ordinary skill would readily ascertain that Deihl fails to disclose "transmucosal absorption of a pharmacologically effective amount through the oral mucosa," which is a requirement of each of the present claims. This is not a trivial matter, because spraying impacts the amount of active compound that can be administered without inducing swallowing. If the amount induces swallowing, there can be no pharmacologically effective amount absorbed through the oral mucosa. Very few actives can be successfully administered through the oral mucosa (Remington's 19th Ed.), much less orally by spray.

Even assuming 100% bioavailability, a patient receiving Deihl's formulation would receive only 4-8 milligrams of active agent, a tiny fraction of what is required for any therapeutic effect. A patient would need to administer a completely unworkable number of spray activations of

Deihl's formulation to realize any potential therapeutic effect, but by that point the volume of fluid sprayed would be so great as to result in swallowing and thus avoid mucosal absorption.

The Office Action also mistakenly compares the weight % of the active in the claimed method to that of the actives in Deihl's example, and concludes that the amounts disclosed in Deihl's example is within a concentration range claimed as therapeutic by Applicant. Office Action at 10. This in no way proves that Deihl's compositions have therapeutic efficacy. The Office Action's reasoning is without merit, because the Deihl actives and the presently claimed actives are different actives, which require different dosages to achieve pharmaceutical efficacy in general and particularly in terms of transmucosal oral absorption.

Deihl's unworkable spray disclosure is quite consistent with the state of the art at the time the present invention was made. As explained below, those skilled in the art generally perceived buccal administration as an ineffective and unworkable delivery method. (See below, discussing REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY, 19th ed. (1995) at 710) Consequently, the disclosure of Deihl itself, as well as the general understanding in the art, were inconsistent with the Office Action's assertions and reasoning that Deihl provides a "general teaching" which one of ordinary skill could apply to extrapolate to diverse pharmaceutical actives, much less to do so with any expectation of success.

At the same time, there can be no dispute that the secondary references do not cure the deficiencies of Deihl, because neither Swaminathan or the PDR discloses any method for treatment involving administering an oral spray, much less doing so in a method that achieves absorption of a pharmacologically effective amount of any active through the oral mucosa.

In actuality, the Office Action is based, first, on improperly ignoring Applicant's claim language, and second, on an unfair reading of Deihl as a "general disclosure" regarding acetaminophen and ibuprofen which can be extrapolated to entirely different actives. Any such reading of Deihl is improper. Deihl does not fairly disclose transmucosal absorption of a pharmacologically effective amount for its own actives. Consequently, none of the cited references

discloses transmucosal absorption of a pharmacologically effective amount of any active compound via oral spray and, for at least this reason, the § 103 rejection is improper and should be withdrawn.

Claims 1-8, 10, 22-26, 28, 40-46, 48, 57-59, and 61 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Fu (WO9303751) in view of Physician's Drug Reference (PDR). This rejection is respectfully traversed.

The Office Action asserts that "Fu teaches sublingual delivery of formulations comprising a therapeutic agent, particularly polypeptides." Office Action at 11 (emphasis in original). From this vague reference to "therapeutic agents," the Office Action concludes that Fu is a "general teaching" from which one of ordinary skill would expect that completely different active compounds could be successfully administered via oral spray. This is not consistent with any fair reading of Fu itself or the state of the art at the time of the present invention. Fu shows that it is limited to two particular, closely related, peptide actives that cannot be administered through the GI tract. This is consistent with the state of the art that buccal dosage forms have been disfavored and only possible for a very limited set of actives.

At the time of the present invention, the art perceived buccal administration as ineffective and unworkable. For example, REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY, 19th ed. (1995) at 710, states that "Only a few drugs may be given successfully by this route" (emphasis added). When a buccal spray is used, the problems of buccal delivery become even greater. Given the variables of (1) different transmucosal absorption rates for different actives, (2) different bioavailabilities of different actives, (3) different potencies and therapeutic dose/efficacy levels, (4) limitations imposed by buccal delivery generally and, in particular, (5) limitations imposed by buccal sprays where the entire volume is present at once and can induce swallowing, thus limiting buccal absorption, the Office Action's assumption that any active could be substituted from the PDR is plainly wrong.

This accepted view of buccal administration was based in part on the belief that the relatively rapid clearing of the mouth by swallowing limited the buccal absorption phase to between

about 5-10 minutes. Therefore, it was understood that the amount of drug delivered would be very small causing the blood plasma levels of dugs administered buccally to rise slowly. Thus, buccal administration was generally disfavored, and thought to be an ineffective and unworkable method of treatment. Consequently, the disclosure of Fu itself, as well as the general understanding in the art, were inconsistent with the Office Action's assertions and reasoning that Fu provides a general teaching which one of ordinary skill could have applied to entirely different pharmaceutical agents, much less to do so with any expectation of success in achieving the presently claimed "transmucosal absorption of a pharmacologically effective amount of the active compound through the oral mucosa," via buccal spray administration.

Fu refers only to delivery of specific polypeptides that are degraded by conventional oral administration. Fu is directed to the administration of these polypeptides because they cannot be ingested. This further underscores the general state of the art regarding the problems with buccal delivery, as described by Remington.

Moreover, unlike Fu's actives, the presently claimed active can be successfully administered by oral ingestion. Therefore, one of ordinary skill in the art would not have been motivated to modify Fu with the pharmaceutical actives of the PDR, or have any reason to believe that such a combination would have had any expectation of success in achieving "transmucosal absorption of a pharmacologically effective amount of zolpidem through the oral mucosa" by spraying the oral mucosa.

The Office Action asserts that, based on the Applicant's "many co-pending applications, it is obvious that many different active agents can be included in the same formulation base and successfully sprayed in the oral mucosa." Office Action at 11. The Office Action's reference to Applicant's co-pending applications is an inappropriate basis for rejection of the instant claims. None of Applicant's co-pending applications is prior art to the pending claims. Nor are all of the formulation bases the same for each active.

The Office Action also incorrectly asserts "various references e. g., Deihl, Fassberg, Cassidy et al, 1993, Controlled Buccal Delivery of Bupenorphine (copy provided), have shown that many different active agents such as analgesics, polypeptides, antibiotics, etc., can be successfully delivered to the buccal mucosa. Also there [allegedly] is no criticality disclosed by the Applicants in spraying...." Office Action at 11. First, the pending method of treatment claims each require "spraying the oral mucosa." This provides the active compound in a fast onset of action and convenient way and provides a significant benefit to patients in need of a quick and convenient pharmaceutical product. This was not foreseen by the cited references. The Fassberg and Cassidy references do not disclose spraying any active pharmaceutical compound on the oral mucosa.

Moreover, the correct basis for ascertaining reasonable expectation of success is not whether an active compound can simply be "administered to the buccal mucosa" (Office Action at 11), but rather whether, upon spraying the composition on the oral mucosa, the active is absorbed through the mucosa to deliver a pharmacologically effective amount of the active to the systemic circulation, as required by the present claims. As established hereinabove, the Deihl reference is not successful even by its own standards, much less by any objective measure as would be applied by the ordinarily skilled artisan. Achieving this by an oral spray composition containing the claimed actives was not suggested or foreseen by the prior art.

None of the art teaches transmucosal absorption of a pharmacologically effective amount of zolpidem by spraying the oral mucosa and none shows faster onset or lower dose requirements, as presently claimed for the zolpidem buccal spray methods. The state of the art, including Remington, teaches away from the Applicants' invention. Remington established that the state of the art was that "only a few drugs may be given successfully by [the buccal] route." Applicants have discovered unexpected results from their use of buccal sprays which further supports the non-obviousness of the claimed invention. See, e.g., specification at paragraph [0006] and [0031].

In summary, none of the rejections establishes a prima facie case of obviousness for all of the reasons set forth above. Moreover, the evidence provided by the specification and the Blondino Declaration would overcome any such prima facie case.

Applicants respectfully request that the rejections be withdrawn in view of the arguments herein, the Blondino Declaration, and the amended claims.

Double Patenting

Claims stand rejected on the grounds of non-statutory obviousness-type double patenting and also as being provisionally rejected over claims of several co-pending applications. As the claims of the present application, as well as those of the co-pending applications are subject to change, Applicants respectfully request that these rejections be held in abeyance until such time as this application is otherwise in a condition for allowance.

Except for the double patenting issues, each of the presently pending claims in this application is believed to be in a condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims. Should the Examiner believe that anything further may be requested to place this application in even better form for allowance, the Examiner is cordially invited to telephone the undersigned attorneys for Applicants.

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